Environmental Health Perspectives
Vol. 11, pp. 47–52, 1975

Low Molecular Weight Components of Polymers Used in Packaging

by Seymour G. Gilbert*

The increasing use of polymers in packaging of foods and drugs focuses attention on the possible chronic toxicity relations of migrants from these polymers to the contents. Such migrants can arise from residues and additives in the polymers from manufacturing processes used in fabrication of packages. The origin and chemical nature of potential migrants, the methods of transfer, and principles involved in development of safety criteria for their regulation are discussed.

The technology of highly developed nations is related to the large-scale automated production coupled with long distribution channels. Packaging is an integral and growing part of this system, particularly as it makes possible both the extended storage requirements for chemical stability and often the physical rigors of the distribution system itself.

The criteria used for insuring safety in packaged materials, particularly foods and drugs, must be concerned with the interactions of the container and products over lengthening period of contact prior to end usage.

As packaged foods become dominant in our daily diet, the emphasis must shift to the possible accumulation of materials producing chronic toxicity rather than to the more easily determinable acute toxicity produced by a single ingestion.

The corresponding safety considerations for drugs and medical devices also apply but with additional concerns related to efficacy.

Another major concern has been the marked increase in the amount and diversity of materials used in packaging. The increased design capabilities of polymeric materials as shown in the lightweight, flexible, or thremoformed package has multiplied greatly the new chemical substances capable of migration.

The corresponding benefits to the public, however, should not be disregarded. These packaging developments have made possible important, if not critical, advances in amounts and safety of our food and drug supply. To abandon these advantages for a return to the simpler systems of the "good old days" could produce perhaps catastrophic impairment of our economy with substitution of acute problems for ones of possible chronic or long-range nature.

*Elimination of the highly centralized manu*facture of drugs and medical devices made possible by the stabilization effects of packaging and its replacement by a return to local manufacture would probably prevent adequate quality control and regulations of safety in the multitude of small firms trying to cope with the advanced technology.

The problem is definition of the potentials for chronic toxicity in terms amennable to adequate regulation even if such regulation further increases centralization of manufacture. Fortunately, the basic principles have been stated clearly for over sixteen years (National Research Council Publication 645 in 1958). These principles state that: "In order to appraise the safety of packaging materials for use in contact with foods, it is necessary (1) to know whether or not any of the container components are leached into the contacted food, (2) to determine the amount of container extractables in the food, and (3) to identify the materials that are extracted. If no material,

* Department of Food Science, College of Agriculture and Environmental Science, Rutgers University, New Brunswick, New Jersey 08903.

or only a toxicological insignificant amount, is transferred to the food, obviously no safety problem exists."

The existing legislation on packaging is largely centered in Subpart F of Section 121 of the Federal Food, Drug and Cosmetic Act as amended in 1958.

These concepts have been extended to packaged drugs and related materials with two common salient factors requiring quantification: (1) toxicological potential, both acute and chronic, of materials entering into possible contact with packaging material for products ingested or contacted by consumers; (2) migration potential, i.e., the transfer of such substances to the drug or other medical device under the condition of packaging, distribution, storage and end use.

Packaging materials are items of commercial manufacture. They are not laboratory chemicals of high purity kept out of contact with modifying agents. They are subjected to a wide range of conditions in their manufacture and conversion to the final packaging form. The materials themselves are mixtures in a composite structure. The migrating component may be a derivative of the starting materials as a result of processing and as such of quite different toxicological properties.

For a given toxicological index, the basic criterion for safety is the potential for migration of specific materials both from the food or drug contacting surface. Moreover, since migration can also occur from other parts of a composite package to the contacting layer, the packaging material must be tested in its end use form to determine whether adequate barriers to such migration are present in the composite.

The problem of potential migration of substances in the finished package can be divided into the two areas of polymeric and nonpolymeric materials. The polymeric materials either directly contact the food or provide functional properties to the overall package; the nonpolymeric materials are usually adjuncts which also often have the greatest potential for migration.

The contacting layer is often the sealing medium in many flexible packages. The other layers generally provide physical protection or barrier properties. The outermost layers may provide the graphic features relating to information sales appeal.

The layers which provide physical barrier and sealing properties are almost invariable high molecular weight polymers and as such are intrinsically odorless, tasteless, and nontoxic. Those packaging materials which do not have these desirable safety characteristics generally have as either accidental or deliberate additives some nonpolymeric substances which are often responsible for any adverse odor, taste, or possible toxicity in end use. Such components can include unreacted monomers or incompletely polymerized fractions, catalysts, stabilizers, functional adjuncts for surface properties such as slip, antiblock, and antifog.

These deliberate additives are covered by identification and listed as allowable with the appropriate base material in the regulation of Subpart F of the FDA regulations.

The determination of lower molecular weight residues is often made by direct analysis of the readily soluble fraction of the polymer as an unfabricated resin. Food grade materials have standards based on analyses of typical polymers with appropriate specifications given in pertinent regulations based on toxicology and potential transfer as provided by the manufacture for his specific product produced by a defined process.

In commercial operations very few, if any, of these qualifying tests are applied to other than large batches of polymer as obtained from the reactor. They are certainly not part of the normal quality assurance tests used in the converter's purchase specifications or production control. Yet tons of product are made daily and shipped to food packages as "food grade" packaging material. Is there a danger to the public in this type of control? It certainly contrasts strongly with the type of batch certification used for drugs.

Informed consideration of the problem shows no cause for alarm when good manufacturing practices are used by the converter to provide a consistently functional packaging material of a specified food grade. It must be first emphasized that whereas drugs are employed as reactive chemicals in human metabolism, packaging materials are used to prevent or minimize change, i.e., they function primarily by their inertness to chemical change. Secondly, the quality of packaging materials is controlled by

various functional tests. These include attributes such as tensile strength, impact resistance, fold endurance, moisture and gas penetration rates, and resistance to various liquids. Other functional tests are sealability, slip, blocking, and packaging machine performance.

In many cases, these properties are determined by the base polymer and are adversely affected by undue amounts of lower molecular weight fractures. Excessive temperature in extrusion of polyethylene, for example, would result in polymer cracking and/or oxidation, lower tensile strength, chemical resistance and lead to films with poor slip and blocking properties.

Poor compounding practices would show up in various physical properties, such as lowered tear resistance and poor clarity from inhomogeneities.

When the packaging material is a composite of layers of various materials, it is put together by adhesives or primers and may have added solvent-based coating, lacquers, and inks.

Many of these additional materials either are, or contain, appreciable amounts of reactive, low molecular weight materials. It is poor practice to have significant contact between such materials and the food itself. For example, reverse-printed inks should not be in direct contact with food, even when approved food colors are used. Overlaquering of the inks does not usually provide an adequate barrier because of incomplete coverage in a lacquer application. Adhesives may contain highly reactive and even toxic components which become inert on cure.

While theoretically an ink and lacquer combination made entirely of all food approved ingredients would comply with the regulations, it would be better and often more economical to use an integral polymeric barrier film in direct contact with the food.

The question then arises as to the effectiveness of any continuous film as a barrier. This question is particualrly important with the low molecular weight residues from the various solvent-based formulations used in making a multilayer printed package.

Modern packages, with their requirements for long shelf life, are often provided with components of high barrier properties. In the cases where these barriers are not the food contacting surface, they also hinder passage of materials to the outside of the package and thus can promote a one-way passage to the food by excluding losses to the exterior.

Many of low molecular weight adjuncts have a characteristic odor or impart characteristic taste notes to a food. Examples are formaldehyde in anchor resins, polyfunctional amines, organic acids, or monomers in reactive coatings. Hydrocarbons, ketones, alcohols, and esters as main components of printing ink systems may appear, accompanied fortuitously by traces of odiferious contaminants like unsaturated hydrocarbons or aldehydes.

Fortunately, the human senses of smell and taste often show very high sensitivity to the presence of such volatiles. In most cases, the threshold for sensory detection is considerably below the toxicological acceptable minimum for the specific material. We find (*1*) that most solvents used in ink and adhesive formulations have sensory thresholds substantially below their toxicological significant level. Thus toluene, ethyl acetate, various aldehydes and ketones range in sensory threshold from the parts per milliion to the parts per billion level. The regulatory problem here is mitigated by the potential for economic damage from off-taste and odor in packaged goods.

The advent of sensitive, reproducible analytical methods of detection of these traces of solvent residues (*2,3*) has so completely replaced sensory evaluations in control of such residues in commercial products so that this is no longer a major concern (*2,4*). Uncured reactants also display adverse function such as poor bond or chemical sensitivity which prevents their undue presence.

For all new polymers, the FDA has established allowable additives for obtaining various specific attributes. Thus permissible antioxidants, surface-active agents, and plasticizers are defined in kind and amount for each such polymeric material. In addition, the agents used in manufacture of these materials—the catalysts, chain extenders, and stoppers, emulsifiers, etc., used in polymerization are now under specific regulation.

For these substances, the major problem is control over mishaps, such as undue excesses in the final product. European thought on this issue generally favors a total or so-called "global" extract value for defining the upper limit of such additives (*5*).

This limit is based on the weight of organic matter in a model extractant used in direct contact with the packaging material. While simple in principle, it has proved controversial in application. The problem centers around selction of one or more model extractants and in defining extraction conditions. The complexity of interaction of extractant with packaging material has hindered adoption of standards from this approach.

An alternate to this is the "market basket" concept used by the U.S. authorities. Here the emphasis is on control of the permissible additives with analytical controls of the foods and related packaged goods in the normal marketing channels. If any undue amount of toxicologically significant materials appear, the source is then traced. An example is the undue presence of PCB's (polychlorinated biphenyls) in samples of food which were traced to the presence of these compounds in paperboard made from recycled paper.

The manufacturer of specific products can and should routinely check his materials by an appropriate model extractant. Thus oily foods and cosmetics can be simulated by a hydrocarbon like hexane. While there is considerable objection (*5*) to the use of a hydrocarbon as a simulant for a fatty acid glyceride, the test if made routinely will determine if unusual amounts of additives are present. If examination of the residues by chromatographic or spectrophotometric methods is also employed, a high degree of assurance can be obtained.

If the material is volatile, generally little or no danger is present when the additive produces a characteristic change in the odor and/or taste of the packaged food at levels appreciably below the threshold for chronic toxicity. For most of the volatile residues in packaging materials the problem of sales acceptance is usually much more acute than that of safety.

The newer polymers, such as polypropylene and some copolymers, have had long-term feeding trials as well as acute toxicity tests of both polymer and low molecular weight additives. More recently, attention has been drawn to the older and more widely used polymers such as poly(vinyl chloride) and its copolymers from the findings of a possible causative factor in angiosarcoma associated with vinyl chloride monomer (VCM). The published toxicity data are limited to inhalation and at exposure levels considerably above those likely to be found from migration, but the possible relation of VCM to carcinogenesis poses two problems. The first concerns chronic exposure of a potential carcinogen at any level and the second relates to the legal questions arising from the Delaney clause which bans the use of any material having any amount of a known carcinogen. The critical question is "How much is zero?"

For the past ten years, we have engaged in research on the migration of low molecular weight additives from packaging materials to the contained product. This work arose from two closely related problems: (1) production of adverse tastes and odors in packaged foods or drugs, and (2) transfer of substances of toxicological significance classifiable as indirect food additives by FDA regulations.

In the first area, we have dealt mainly with residual solvents and allied contaminants of very low sensory threshold. Thresholds define concentrations at which there is no measurable effect detectable in a biochemical frame of reference and can be considered as the limiting concentration for occurrence of a chemical reaction required for sensory preception.

Methods were developed (*3*) for analysis of specific residues in the range of 10^{-6} to 10^{-9} of mass ratios of residual concentrations in the packaging material and in the contained food to provide correlation with psychometric evaluations. The analytical methods enabled direct determination of partition or transfer of these migrants.

In the second area, we have measured migration rates and migration mechanisms (*6*) of known additives to polymers such as organotin in PVC from container to food and food simulating solvents.

In the course of this work, we have become aware of the nonlinear relation of partition at very low concentrations of migrant in the polymer. The determined transfer rate was found often to become essentially zero in real time at measurable but low concentrations in the polymer. This is related also to the equilibrium value in simulated solvent studies whereby very low levels of migrated material prevent further transfer from solid to liquid phase.

The zero effective transfer is probably related to the diffusion of small molecules in slabs of macroscopic dimensions where strong inter-

actions create diffusion shells involving an approach to infinite transfer time. An example of this effect is the extremely slow permeation of oxygen through a dry collagen film compared to the corresponding hydrated film where a given mass flow in dry film may require years versus seconds in the wet one (*7*).

These zero effects are closely akin to consideration involved in migration of additives considered potential carcinogens. The sensory threshold effect is relatable to an ineffective level of biochemical reaction, while the migration lags are also important in evaluating risks involved in the transfer in a given time frame of human life of sufficient reactant to produce the biochemical events in carcinogenesis.

We have begun to apply these methods and considerations to the VCM problem. In a preliminary way, we can either postulate a no-effect threshold on the basis of concepts of Hutchinson (*8*) and Dinman (*9*) who place this level at 10^4 atoms per liver cell. We have calculated that this is equivalent to 1.5×10^{-10} g/g of tissue (see appendix for calculation).

We can also use the limited data on inhalation of VCM which suggests no measurable effect at levels of exposure in air of 50 ppm over ten years period as productive of angiosarcoma. To be conservative, we will reduce this exposure to a dosage of 1 ppm per day for 10 years.

These two postulates are used to estimate the probability of risk from VCM present in packaged materials. The boundary conditions and calculations are in the appendix. These calculations show a range of chronic exposure required of from 100 years in the most conservative estimates for humans using high levels of PVC packaged products to 1000 years for more likely conditions.

It is obvious that these are very crude estimates and the lower limit is too close to "real time" for acceptance without further quantification of the relations involved. To this end, we have recently established in our laboratories methods for VCM sensitive and specific at the 10^{-9} level. The method is based on combined GC-mass spcectroscopic isolation and quantification at the two mass ion ratios arising from the natural isotopes of Cl (62 and 64). With three properties of VCM (GC separation, mass, and isotope ratio) we believe we have the specificity needed for examination of transfer to foods and related biological systems.

A paper on this method has been submitted for publication (*10*).

Without entering into the controversy over the single or multiple cause of carcinogenesis, it can be seen from these considerations that the level of risk from ingestion of VCM from packaged foods and drugs is very low from properly regulated commercial sources of PVC.

It becomes important then to examine the risk to human life arising from any hasty and catastrophic changes in our present packaging systems. To ban the use of vinyl chloride copolymers in cans and films would create a real hazard in terms of microbial invasions in improperly protection foods and drugs.

The risk of botulism in foods is ever present. The risks from carcinogens by fungal origin are real and of much greater demonstrated frequency than that from VCM in foods. The risks of sepsis from defective seals in medical devices used in surgery such as sutures has been kept appropriately low only from well-established packaging designs after using PVC.

To advocate substitution of these risks by forcing a choice between scarcities of packaged necessities or improperly evaluated alternates is at least ill-advised. The degree of danger from VCM in packages has to be demonstrated by toxicological data rather than on unsubstantiated theories or legalistic sophistry based on misuse of the Delaney clause. In the interim required for the accumulation of pertinent toxicological data, it would be prudent to pursue a course aimed at reduction and regulation of VCM in packaging materials to low levels. We should also determine the partition factors in actual food packaging systems to properly evaluate the risk factors. These steps are more reasonable than any immediate reduction in the supply of this highly useful packaging material.

Appendix

The risk from exposure to VCM in PVC used for food and drug packaging can be calculated as follows. We define exposure as the product of concentration in the container, partition ratio, frequency of contact per day, and biochemical effectiveness:

$$E = CPFB \qquad (1)$$

where C = concentration in container = 1×10^{-5} g/g to 1×10^{-6} g/g (1–10 ppm), P = partition ratio = 1×10^{-3} to 1×10^{-6} (includes daily food intake and its contact with PVC), F = frequency = 1 to 10 contacts/day, B = biochemical effect = 0.01 to 1 (ratio of ingestion toxicity to inhalation). Thus we have for E, exposure effective grams of toxicant/day = $10^{-6} \times 10^{-3} \times 10 = 10^{-8}$ g VCM/day.

If we can assume an exposure of 1 ppm of air/day for 10 years as an effective zero exposure and inhalation to ingestion ratio of 1 as above,

$$\frac{1 \times 10^{-6} \text{ g/g per day for 10 years}}{1 \times 10^{-8} \text{ g/g per day}} = 10^{3} \text{ years}$$

If we use a very conservative estimate where $C = 1 \times 10^{-6}$ g/g, $P = 1 \times 10^{-3}$, $F = 100$, $B = 1$, then 100 years of exposure are required. At lower frequencies of contact ($F = 10$), or lower biological effectiveness ($B = 0.1$), then 1000 years are required. It is also quite reasonable to expect P will be closer to 10^{-6} at very low concentration of VCM in PVC as a result of nonlinearity of desorption in this region.

Hutchinson's value of 1×10^{4} atoms per liver cell of weight 7×15^{9} g gives, from Avogadro's number and the molecular weight of VCM, 1.5×10^{-10} g VCM/g tissue.

This value as compared to the above calculated range of daily intake of VCM would require complete absorption and accumulation in liver tissue to reach in a lifetime an effective concentration for biochemical effect. In the absence of adequate data on these two factors in VCM action, only speculation can be used, but the risk cannot be considered as very different from the calculations based on the limited toxological data as above.

REFERENCES

1. Wilks, R. A., Jr., and Gilbert, S. G. Sensory and instrumental evaluation in model systems of residues migrating from can coatings. J. Food Sci. 37: 72 (1972).
2. Gilbert, S. G., and Wilks, R. A., Jr. An improved method for determination of residual solvents in packaging materials. Materials Res. Stand. 8 (1): 29 (1968).
3. Morano, J. R., Gilbert, S. G., and Daun, H. Isolation and identification of compounds producing adverse effects in packaged food systems. Paper presented at the 34th Annual I.F.T. Meeting, New Orleans, May 1974.
4. ASTM Standards. Standard method of test for residual solvents in flexible barrier materials. American Society for Testing and Materials, Philadelphia, 1972, F151.
5. Figge, K. Migration of additives from plastics films into edible oils and fat simulants. Food Cosmet. Toxicol. 10: 815 (1972).
6. Yen, W., Gilbert, S. G., and D. H. Kleyn. A study of the migration of organotin stabilizer from polyvinyl chloride films to liquid foods. I. Quantitative migration. II. Qualitative migration. Papers presented at the IARRI Symposium, Munich, Germany, October 1972.
7. Lieberman, E. R., and Gilbert, S. G. Gas permeation of collagen films as affected by crosslinkage, moisture and plasticizer content. J. Polym. Sci. Polym. Symp. Ed., 41: 33 (1973).
8. Hutchinson, G. E. The influence of the environment. Proc. Nat. Acad. Sci. (U.S.) 51: 930 (1964).
9. Dinman, B. D. No-concept of no-threshold: chemicals in the environment. Science, 175: 495 (1972).
10. Rosen, J. D., et al. Analysis of vinyl chloride at the parts per trillion level. Science, in press.